

High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda

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Abstract

Background: Artemisinin-based combination therapies are rapidly being adopted for the treatment of malaria in Africa, yet there are limited data on safety and efficacy among HIV-infected populations.

Methods: We compared malaria treatment outcomes between cohorts of HIV-infected and HIV-uninfected children in Uganda followed for 29 and 18 months, respectively. Malaria was treated with artesunate plus amodiaquine and outcomes assessed using standardized guidelines. HIV-infected children received trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy according to current guidelines.

Results: Thirty-five malaria episodes among 26 HIV-infected participants and 258 malaria episodes among 134 HIV-uninfected children were included. Twelve HIV-infected children were receiving antiretroviral therapy with 11 receiving zidovudine. Malaria treatment was highly efficacious in both the HIV-infected and HIV-uninfected cohorts (28-day risk of recrudescence 0% and 3.6%, respectively) however, there was a trend towards increased risk of recurrent malaria in the HIV-uninfected children (2.9% vs. 13.2% respectively, $p=0.08$). Importantly, the risk of neutropenia 14 days after treatment with artesunate plus amodiaquine was higher in HIV-infected compared to HIV-uninfected children (45% vs. 6%, respectively, $p < 0.001$). All neutropenia episodes in HIV-uninfected children were of mild to moderate severity while 16% of neutropenia episodes in the HIV-infected cohort were severe or life-threatening ($< 750/\text{mm}^3$). Among HIV-infected children, the risk of neutropenia was significantly higher in those receiving antiretroviral therapy (75% vs. 26%, $p=0.001$).

Conclusions: Artesunate plus amodiaquine was highly efficacious for malaria treatment in HIV-infected children, but associated with a high risk of neutropenia, especially in the setting of concurrent antiretroviral use. Our findings highlight an urgent need for evaluation of alternative antimalarial therapies in HIV-infected individuals.

Introduction

Artemisinin-based combination therapy (ACT) is now recommended for treatment of uncomplicated malaria in sub-Saharan Africa. Most African countries have chosen one of two regimens as first-line therapy, artesunate plus amodiaquine (AS/AQ) or artemether/lumefantrine (AL) [1]. AS/AQ is now available as a co-formulated single tablet, and rapidly increased uptake of this treatment is anticipated. However, safety assessment of AS/AQ has been limited.

The safety of artesunate and other artemisinins has been extensively studied, and these drugs appear to be very safe at the dosages used to treat malaria [2, 3].

Amodiaquine has been used to treat malaria for decades, however concerns about safety of this drug remain. When used for malaria chemoprophylaxis, amodiaquine was associated with rare but serious adverse events, including agranulocytosis, aplastic anemia, and hepatotoxicity [4, 5]. These problems led to removal of amodiaquine from the World Health Organization (WHO) essential drugs list in 1990. Subsequent reevaluation led to appreciation that the risk of toxicity with short-term amodiaquine treatment appeared to be lower than that with chemoprophylaxis [6], and amodiaquine is now recommended by WHO for use in combination regimens to treat malaria [7].

The safety of AS/AQ in HIV-infected populations has not been studied. Overlapping toxicities of amodiaquine and drugs commonly used to manage HIV infection such as trimethoprim-sulfamethoxazole (TMP/SMX), and potential drug interactions with antiretroviral therapy merit concern. We therefore compared the efficacy and safety of AS/AQ for the treatment of uncomplicated malaria in a cohort of

HIV-infected children receiving standard HIV care with a cohort of HIV-uninfected children in Kampala, Uganda.

Methods

Study participants

This study included children diagnosed with uncomplicated malaria treated with AS/AQ participating in two parallel cohort studies in Kampala, Uganda. Details of these two cohorts have been published previously and are described here briefly [8, 9]. A total of 601 HIV-uninfected children were recruited into a community-based cohort from a geographically defined census population using probability sampling from November 2004 through April 2005. Eligibility criteria included: 1) age 1 to 10 years, 2) agreement to come to the study clinic for any febrile episode or other illness, 3) agreement to remain in Kampala for the duration of the study, 4) agreement to avoid medications administered outside the study protocol, 5) lack of history of any known serious chronic disease requiring frequent medical attention (e.g. AIDS, sickle cell disease, malignancy), and 6) weight \geq 10 kg. Children in the HIV-uninfected cohort were randomized to receive AS/AQ, artemether-lumefantrine or AQ/sulfadoxine-pyrimethamine at the time of their first episode of uncomplicated malaria. Only children receiving AS/AQ were included in this analysis. Insecticide treated bednets (ITNs) were provided to all participants in this cohort during the period of May-June 2006. Beginning in February 2007, HIV testing was offered to all participants remaining in the cohort using a serial enzyme immunoassay testing algorithm according to national guidelines. We included up to the first 3 treatments with AS/AQ given to participants in the community-based cohort to

match the maximum number of treatments given to participants in the HIV-infected cohort.

A total of 300 HIV-infected children were enrolled from a pediatric HIV clinic from October 2005 through August 2006. Eligibility criteria were the same as for the HIV-uninfected cohort, except for: 1) living within a 20 km radius of the clinic, 2) no restriction based on a history of serious chronic disease, and 3) weight \geq 5kg. All HIV-infected cohort participants were prescribed TMP/SMX prophylaxis and provided with ITNs. Those children meeting WHO eligibility criteria were provided antiretroviral therapy.

Study participant follow-up

Children from both cohorts were followed in separate study clinics open 7 days a week for all of their medical problems using similar protocols. Children who presented with new medical problems underwent standardized medical evaluation. Standardized treatment algorithms were developed to guide therapy for malaria and non-malarial illnesses. Medications with antimalarial activity were avoided for the treatment of non-malarial illnesses. Malaria was diagnosed if a child had fever (documented tympanic temperature \geq 38.0°C and/or history of fever in the previous 24 hours) and any level of parasitemia. Study participants were withdrawn from the study cohorts if they moved out of the study area, could not be located for any consecutive 60 day period, withdrew consent or died.

Treatment of malaria

AS/AQ treatment was directly observed and dosed as follows: amodiaquine (Camoquine; Parke-Davis, USA), 10mg/kg on the first 2 days followed by 5mg/kg on the third day and artesunate (Arsumax; Sanofi-Aventis, France), 4mg/kg for three days. Patients treated for malaria were asked to return on days 1, 2, 3, 7, 14 and 28 or any other day they felt ill.

Follow up evaluation consisted of a standardized history and physical examination. Blood was obtained by finger prick for thick blood smears on all follow-up days, except day 1. Complete blood counts and alanine aminotransferase (ALT) levels were assessed on the day malaria was diagnosed and day 14 of follow-up.

Malaria outcomes and assessment of efficacy and safety of antimalarial therapy

Treatment outcomes were classified according to 2005 WHO guidelines as early treatment failure, late clinical failure, late parasitological failure, and adequate clinical and parasitological response [10]. Clinical treatment failures within the first 14 days were treated with standard doses of quinine. Cases of symptomatic malaria diagnosed more than 14 days after a previous episode were treated with the same assigned treatment regimens the study participants were initially randomized to. Late parasitological treatment failures were not treated unless the patient went on to develop symptomatic malaria. An adverse event was defined as any untoward medical occurrence, irrespective of its suspected relationship to the study medications as per International Conference of Harmonization guidelines. Adverse events were graded as mild, moderate, severe or potentially life-threatening using the National Institutes of Health Division of AIDS tables for grading the severity of adverse events.

Laboratory methods

Microscopy was used to diagnose malaria. Parasite densities were estimated by counting the number of asexual parasites per 200 white blood cells and calculating parasite densities, assuming a white blood cell count of 8,000 cells per μl . Molecular genotyping was used to distinguish recrudescence from new infections as previously described [11]. Complete blood counts (Coulter AcT5diff instrument, Beckman Coulter) and ALT levels (Cobus Integra instrument, Roche) were measured at College of American Pathologists (CAP) certified laboratories in Uganda.

Statistical analysis

Data were double-entered in Access (Microsoft Corporation, Redmond, WA) and statistical analysis was performed using Stata version 8 (Stata, College Station, TX, USA). Pairwise comparisons of categorical variables were made using generalized estimating equations with adjustment for repeated measures in the same patient using exchangeable correlation and robust standard errors. Efficacy and safety data were evaluated using an intention-to-treat analysis. Efficacy outcomes included 28-day risk for recurrent parasitemia, both unadjusted and adjusted by genotyping to distinguish recrudescence and new infection. Risks of treatment failure were estimated using the Kaplan-Meier product limit formula. Data were censored for patients who did not complete follow-up and for new infections based on outcomes adjusted by genotyping. Pairwise comparisons of treatment efficacy for individual episodes of malaria were made using a Cox proportional hazards model with adjustment for repeated measures in the

same patient. To identify risk factors for neutropenia in HIV-infected children treated with AQ/AS we used a logistic model, adjusted for repeated measures in the same patient. In this model, neutropenia of any severity was the dependent variable and previous AS/AQ treatment and antiretroviral therapy were included as independent variables.

To evaluate the clinical consequences of neutropenia after AS/AQ treatment among HIV-infected study participants, we conducted a nested case-control study. We randomly selected 3 controls for each case of neutropenia, matched for ARV treatment, age and CD4 cell counts or CD4 percentage based on age. We compared the prevalence of significant clinical events over the duration of neutropenia in the cases and for the same time period in matched controls using Chi square or Fisher's exact tests. A p-value < 0.05 was considered statistically significant. Significant clinical events were defined as any febrile illnesses, bacterial skin infections, septicemia and pneumonia. Duration of neutropenia was defined as the period from the date AS/AQ therapy was started to the date of the next normal neutrophil value ($>1300/\text{mm}^3$). Routine 3-monthly laboratory evaluations were used to monitor resolution of laboratory abnormalities.

Role of the funding source and ethical approval

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The first author had full access to all study data and had final responsibility for the decision to submit for publication. Ethical approval for both cohort studies was obtained from the Uganda National Council of Science and

Technology, Makerere University Research and Ethics Committee, and University of California, San Francisco Committee on Human Research.

Results

Study participants and baseline characteristics

In the HIV-infected cohort, 26 children were diagnosed with at least 1 episode of malaria over an 18 month period, resulting in 35 treatments with AS/AQ. In the HIV-uninfected cohort 134 children were randomized to AS/AQ, and a total of 258 treatments were included in this study over a 29 month period. Among participants treated for a second or third time with AS/AQ, the median duration between treatments was 133 (range 34-327) and 114 (range 18-649) days for the HIV-infected and HIV-uninfected cohorts, respectively. Of the 134 community-based cohort participants who were treated with AS/AQ, 104 were tested for HIV, and all were negative. For those untested, 21 were excluded from the study (12 moved from study area, 6 unable to locate for > 60 consecutive days, 3 withdrew consent) before testing was offered, and 9 refused testing. A comparison of the baseline characteristics of malaria episodes treated with AS/AQ in the two cohorts are presented in Table 1. All HIV-infected children were receiving TMP/SMX at the time they were treated with AS/AQ, while none of the HIV-uninfected cohort participants were prescribed TMP/SMX. Members of the HIV-infected cohort were slightly older at the time they were treated with AS/AQ, had higher use of ITNs, and had a higher mean ALT at baseline, although the risk of an abnormally elevated ALT at baseline was similar in the two groups (8.5% for the HIV-infected cohort vs. 3.1% for the HIV-uninfected cohort, $p=0.13$). Participants in the HIV-uninfected cohort were

more likely to have received repeated therapies with AS/AQ. Members of the community-based cohort who were tested or not tested for HIV did not differ in the baseline characteristics shown in Table 1 (data not shown).

Treatment efficacy of AS/AQ

Members of both cohorts responded well to treatment for uncomplicated malaria with AS/AQ (Table 2). There was a trend towards an increased risk of recurrent malaria within 28 days in the HIV-uninfected cohort compared to the HIV-infected cohort (13.2% vs. 2.9%, $p=0.08$). However, treatment failures due to recrudescence were uncommon, with a risk of 3.6% in the HIV-uninfected cohort and 0% in the HIV-infected cohort ($p=0.25$). Times to fever and parasite clearance were also similar for the two groups (Table 2).

Safety and tolerability of AS/AQ

New or worsening cough was more common in the HIV-infected cohort during the 14 days following therapy with AS/AQ, but other clinical events were similar in the two cohorts (Table 3). Neutropenia 14 days after therapy was significantly more common in the HIV-infected cohort (45%) than in the HIV-uninfected cohort (6%, $p < 0.001$). Neutrophil counts were normal ($>1300/\text{mm}^3$) prior to initiation of therapy for all subjects who developed neutropenia. The risk of anemia, thrombocytopenia, and elevated ALT did not differ between the cohorts. All neutropenia episodes in the HIV-uninfected cohort were of mild or moderate severity (median= $1080/\text{mm}^3$; range 760- $1300/\text{mm}^3$), while 16% of HIV-infected participants developed severe or life-threatening neutropenia (median= $560/\text{mm}^3$; range 400- $680/\text{mm}^3$). Compared to the HIV-uninfected cohort, HIV-

infected children treated with AS/AQ had over 7 times the odds of neutropenia of mild severity or greater and over 24 times the odds of neutropenia of moderate severity or greater (Table 4).

Among the 31 HIV-infected children who received AS/AQ and in whom neutrophil values were available, 12 (39%) were receiving antiretrovirals concurrently. The risk of neutropenia following therapy with AS/AQ was higher in those taking antiretrovirals compared to those not taking antiretrovirals (75% vs. 26%, $p=0.001$ after controlling for prior AS/AQ therapy). All but one of the study participants on antiretroviral therapy were receiving zidovudine ($n=11$) the antiretroviral most closely associated with bone marrow suppression. There was also a trend towards a higher risk of neutropenia among HIV-infected children treated with AS/AQ for the second or third time compared to those receiving their first treatment (75% vs. 35%, $p=0.11$ after controlling for antiretroviral use) (Table 4).

To assess the clinical significance of neutropenia, we compared the risk of significant clinical events in HIV-infected children during the period of neutropenia to HIV-infected controls not treated with AS/AQ over the same time. There was a trend towards a higher risk of any significant clinical event in subjects treated with AS/AQ (57% vs. 35%, $p=0.16$). The risk of pneumonia was higher in subjects treated with AS/AQ with neutropenia compared to controls (43% vs. 19%, $p=0.008$). None of the episodes of pneumonia diagnosed during this risk period required hospitalization.

Discussion

Our results show that, in Uganda, AS/AQ was efficacious for the treatment of uncomplicated malaria in both HIV-infected children receiving TMP/SMX prophylaxis and in HIV-uninfected children. However, among the HIV-infected children, treatment with AS/AQ was associated with a remarkably higher risk of neutropenia compared to HIV-uninfected children. HIV-infected study participants with concurrent antiretroviral use or a history of repeated doses of AS/AQ had the highest risk of neutropenia. This neutropenia appeared to have clinical consequences, as HIV-infected study participants had an increased risk of pneumonia during neutropenic episodes compared to matched controls.

Neutropenia associated with AS/AQ treatment was most likely due to AQ. Artemisinins have excellent safety profiles [3], and the addition of artesunate to other drugs does not appear to adversely affect safety and tolerability [2, 12]. In contrast, neutropenia is a well documented, albeit uncommon adverse effect associated with AQ [6]. AQ and its metabolites exhibit cytotoxic effects on mononuclear leukocytes and inhibit granulocyte-monocyte colony formation [13]. Rates of serious toxicity with AQ when used as chemoprophylaxis were reported as 1:2100 for blood dyscrasias and 1:31,000 for deaths from blood dyscrasias [14]. However, short-term AQ treatment for malaria is generally considered safe [6]. The 6% risk of neutropenia observed in our HIV-uninfected cohort is consistent with prior studies of AQ safety [6, 12]. However, in our HIV-infected cohort, the 45% risk of neutropenia, including a 16% risk of severe neutropenia, is cause for concern.

In addition to AQ use, several other factors may have contributed to the high risk of neutropenia seen in our HIV-infected children. HIV infection is associated with hematological disturbances, possibly due to viral inhibition of hematopoietic precursor cells or infections with other pathogens [15]. Neutropenia has been reported in 10-50% of HIV-infected individuals,¹⁶ with the risk increasing with increasing immunosuppression [15]. In addition, use of concomitant medications likely contributed to neutropenia. Neutropenia is one of the most commonly reported adverse reactions associated with TMP/SMX prophylaxis [17, 18]. Different antiretroviral drug classes are independently associated with blood disorders [19]. Nucleoside reverse transcriptase inhibitors have been associated with hematological events. Zidovudine in particular is associated with increased risk of neutropenia in children and adults [20]. Finally, pharmacological interactions between antiretrovirals, TMP/SMX and AQ may have potentiated AQ toxicity. Recent studies have shown that efavirenz is an inhibitor of CYP2C8, a hepatic enzyme necessary for AQ metabolism [21], and that concomitant administration of efavirenz and AS/AQ is associated with increased AQ exposure [22]. Trimethoprim has also been shown to inhibit CYP2C8 [23].

In adults, HIV and increasing immunosuppression are associated with diminished antimalarial treatment response and an increased risk of recurrent infection after antimalarial therapy [24-26]. However, little is known about the effect of HIV on antimalarial efficacy in children, the population most vulnerable to malaria. We compared the efficacy of AS/AQ in HIV-infected and -uninfected children. No recrudescence of malaria occurred in HIV-infected children treated with AS/AQ. There was a trend toward more recurrent malaria due to reinfection within a month after AS/AQ

therapy in HIV-uninfected children, presumably because this cohort did not receive TMP/SMX prophylaxis and widespread ITN administration. Thus, there was no evidence of diminished efficacy of AS/AQ in HIV-infected children and, as recently described, administration of TMP/SMX and ITNs appeared to offer protection against malaria [9].

Our study had some limitations. The low incidence of malaria in our HIV-infected cohort limited the number of AS/AQ treatments and the precision of our estimates. However, given the strong association between HIV infection and neutropenia after AS/AQ use, these results were highly statistically significant. We did not test 22% of community-based controls for HIV, as they had either been excluded from our cohort prior to testing or declined to be tested. However, the lack of HIV infection among any of the 104 children who were tested suggests that very few of the community cohort, if any, had this infection. Any bias resulting from misclassification of HIV status would be expected to underestimate differences seen between the HIV-infected and community cohorts.

The findings of this study could have major implications regarding malaria treatment recommendations in Africa. AS/AQ has been chosen as first line antimalarial therapy in 15 countries in Africa and in several other countries, including Uganda, AS/AQ is the alternative first-line antimalarial therapy after AL [1]. TMP/SMX prophylaxis is now recommended for all HIV-infected Africans by many authorities, and it is increasingly being implemented. Similarly antiretroviral therapy is increasingly available to HIV-infected Africans. Our findings suggest that in HIV-infected individuals, particularly among those receiving zidovudine-containing antiretroviral therapy, the treatment of malaria with AS/AQ should be avoided if at all possible. As

alternatives, AL has proven efficacy, without known serious toxicity risks [8, 17], and dihydroartemisinin-piperaquine has recently shown excellent efficacy [28-30]. However, other antimalarial drug combinations may also lead to toxicity due to HIV-specific factors or drug interactions, and research on the safety of malaria therapies in HIV-infected Africans is an urgent priority.

Contributors

M. Kamya, D. Havlir, P. Rosenthal, G. Dorsey, E. Chalebois, S. Staedke, A. Kekitiinwa, and A. Gasasira contributed to the design of the studies. All authors assisted with interpretation of the data and preparation of the manuscript. M. Kamya, J. Achan, T. Mebrahtu, S. Staedke and A. Gasasira supervised enrollment and follow-up of study participants and directed the clinical studies. M. Kamya, D. Havlir, E. Charlebois, T. Ruel, P. Rosenthal and G. Dorsey, J. participated in the oversight of study activities. J. Kalyango supervised antimalarial prescriptions and dispensing for the HIV-infected cohort, G. Dorsey and A. Gasasira verified and analyzed the data. All authors appraised and approved the final report.

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Conflict of interest statement

We declare that we have no conflict of interest

References

Table 1. Baseline characteristics on day malaria diagnosed for individual treatments

Variable	HIV-uninfected cohort (n=258)	HIV-infected cohort (n=35)	p-value
AS/AQ treatment episode, n (%)			
1 st	134/258 (52%)	26/35 (74%)	
2 nd	76/258 (29%)	7/35 (20%)	0.03
3 rd	48/258 (19%)	2/35 (6%)	
Age in years, mean (SD)	6.3 (2.5)	7.2 (3.2)	0.05
Weight in kg, mean (SD)	19.8 (6.3)	20.2 (6.8)	0.69
ITN use, n (%)	42/258 (16%)	31/35 (89%)	<0.001
Tympanic temperature °C, mean (SD)	37.9 (1.2)	38.2 (1.1)	0.22
Geometric mean parasite density (range)	10152/μL (32-735560)	6810/μL (16-428440)	0.37
Parasite species, n (%)			
<i>P. falciparum</i> alone	245/258 (95%)	30/35 (86%)	
<i>P. falciparum</i> mixed infections	2/258 (1%)	1/35 (3%)	0.08
Non-falciparum infections	6/258 (2%)	1/35 (3%)	
Unable to determine species	5/258 (2%)	3/35 (9%)	
WBC per mm ³ , mean (SD)	7383 (3469)	6445 (3371)	0.13
Neutrophils per mm ³ , mean (SD)	4302 (2806)	3487 (2428)	0.11
Platelets per mm ³ , mean (SD)	218516 (92692)	197514 (121301)	0.23
Hemoglobin gm/dL, mean (SD)	11.7 (1.4)	11.8 (1.3)	0.52
ALT (SGPT), mean (SD)	21.2 (17.0)	30.3 (27.1)	0.006

Table 2. Response to malaria therapy with AS/AQ according to HIV status

Outcome	HIV-uninfected cohort (n=258)	HIV-infected cohort (n=35)	p-value
28 day WHO classification, n (%)			
Adequate response	217/258 (84%)	33/35 (94%)	
Early treatment failure	2/258 (1%)	0	
Late clinical failure	19/258 (7%)	0	
Late parasitological failure	12/258 (5%)	1/35 (3%)	
Outcome not assessed	8/258 (3%)	1/35 (3%)	
Risk of early failure or recurrent infection [†] (95% CI)	13.2% (9.6-18%)	2.9% (0.4-18.6%)	0.08
Risk of early failure or recrudescence ^{†*} (95% CI)	3.6% (1.9-6.9%)	0	0.25
Fever clearance, n (%)			
Documented fever day 1	10/255 (4%)	4/35 (11%)	0.05
Documented fever day 2	2/253 (1%)	1/34 (3%)	0.28
Documented fever day 3	3/254 (1%)	0/34 (0%)	-
Parasite clearance, n (%)			
Positive smear day 2	9/252 (4%)	2/34 (6%)	0.48
Positive smear day 3	0/254 (0%)	0/34 (0%)	-

[†] Kaplan-Meier product limit formula

* PCR-corrected

Table 3. Risk of new or worsening adverse events within 14 days of AS/AQ therapy

Adverse Event	HIV-uninfected cohort	HIV-infected Cohort	p-value
Common symptoms			
Cough	64/257 (25%)	19/35 (54%)	<0.001
Anorexia	65/257 (25%)	7/35 (20%)	0.53
Weakness/malaise	44/257 (17%)	9/35 (26%)	0.24
Abdominal pain	45/237 (19%)	6/35 (17%)	0.77
Vomiting	37/257 (14%)	4/35 (11%)	0.66
Pruritis	26/257 (10%)	3/35 (9%)	0.95
Diarrhea	19/257 (7%)	3/35 (9%)	0.91
Laboratory values			
Neutropenia	15/253 (6%)	14/31 (45%)	<0.001
Thrombocytopenia	1/250 (0.4%)	0/34 (0%)	-
Anemia	10/256 (4%)	3/34 (9%)	0.13
Elevated ALT	2/255 (0.8%)	0/34 (0%)	-

Table 4. Risk factors for new or worsening adverse events due to neutropenia

Increases in neutrophil count severity score	HIV-uninfected cohort	HIV-infected cohort
None	238 (94%)	17 (55%)
Mild (1000-1300/mm ³)	12 (4.7%)	5 (16%)
Moderate (750-999/mm ³)	3 (1.2%)	4 (13%)
Severe (500-749/mm ³)	0	3 (9.7%)
Life-threatening (< 500/mm ³)	0	2 (6.5%)
Associations between HIV and adverse events due to neutropenia		
Outcome	OR (95% CI)*	p-value
Adverse event of mild severity or greater	7.6 (3.9-15.0)	<0.001
Adverse event of moderate severity or greater	24.6 (6.8-89.1)	<0.001
Risk factors for adverse events due to neutropenia among HIV-infected patients		
Risk Factor	OR (95% CI)*	p-value
Prior treatment with AS/AQ	1.6 (0.9-2.9)	0.11
Antiretroviral use	2.3 (1.4-3.6)	0.001

* Generalized estimating equations with adjustment for repeated measures in the same patient.